REMARKS

Favorable action on the merits is solicited in view of the following remarks.

I. Claim Status and Amendments

Claims 20, 25, 69-70, 72, 75, 82-91, 100, and 102-105 presently appear in this application. No claims have been allowed.

Claims 20, 25, 72, 84, and 89 have been withdrawn.

Claims 69, 70, 75, 82, 83, 85-88, 90, 91, and 102-105 have been examined on the merits and stand rejected. Claims 69, 70, 75, 82, 83, 85-88, 90, 91, and 102-105 are also objected to. These claims define patentable subject matter warranting their allowance for the reasons discussed herein. Applicants have not amended the claims by way of the present response.

On page 2 of the Office Action, the Examiner noted the presence of typographical errors in the response filed March 24, 2009. Applicants appreciate the Examiner's efforts to examine the case despite the noted errors, which appear to be the result of a technical problem associated with scanning and/or electronic filing of the response.

II. Claim Objections & Withdrawn Claims

On page 2, the Examiner objected to claims 69, 70, 75, 82, 83, 85-88, 90, 91, 102-105 to for reciting non-elected

subject matter, there being no allowable generic or linking claim.

Not withstanding this objection, these claims are being left to remain in the case as it is believed that the elected species have now been shown to be allowable and therefore, the generic or linking claims should now be examined in this case.

Furthermore, Applicants again respectfully ask the Examiner to consider rejoining and examining the withdrawn claims, as there would not be any additional burden for the Examiner to perform a complete search and examination of these claims, due to related and overlapping subject matter in both claims, the subject matter in the withdrawn claims has basically already been searched and examined previously. Note that even when claims are restrictable, they may be examined together if doing so would not create significant additional burden on the part of the Examiner.

To this end, kindly note that withdrawn claim 20 corresponds to examined claim 69, except the polypeptide in claim 20 is the entire NIK, whereas in claim 69 it is a NIK fragment comprising the cyc binding domain (SEQ ID NO: 18). Similarly, it should be noted that SEQ ID NO: 19 (c-terminus NIK 624-947) of the non-elected claims comprises elected SEQ ID NO:18 (NIK 640-720). As such, it is believed that it would not create an undue burden to search and examine the non-elected claims along with

the elected invention, given the related and overlapping subject matter.

III. Enablement Rejection

Claims 69, 70, 75, 82, 83, 85-88, 90, 91, and 102-105 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the reasons set forth on pages 2-5 of the Office Action.

This rejection is respectfully traversed for the same reasons set forth in the response filed March 24, 2009 (which arguments are reiterated herein by reference) and for the following reasons.

The present application relates to the use of NIK and related molecules for binding to cγc and inhibiting cγc/NIK interaction, thus modulating signal activities controlled by cytokines and NIK induced NF-κB activation, and thereby treating diseases in which NIK/cγc interaction is involved (claim 69) or in which NF-κB activation is involved (claim 70). Beginning at page 5, line 16, through page 7, line 15, the specification describes in detail the evidence and role of NF-κB in pathogenesis of human disease. Further, the disclosure and the examples of the instant application establish that cγc and NIK interaction induces NF-κB activation and that inhibition of cγc/NIK interaction inhibits NIK mediated NF-KB activation. See,

for instance, page 20, line 9, up to page 21, line 4, page 21, lines 22-23, and all of the examples in the specification.

Accordingly, as it has been shown in the present specification that the polypeptides used in the present method interfere with NIK/cyc interaction, the type of disease that can be treated in accordance with the present invention is adequately defined in claim 69. Accordingly, all diseases mediated by NF-κB are necessarily diseases in which NIK and cyc interaction is involved in the pathogenesis of the disease. For this reason, it is believed that there is enabling support and written description support in the specification for the treatment of such diseases by the polypeptides as defined in claim 69. The same is believed to be true with respect to claim 70, which corresponds to claim 69 but recites "treatment of a disease in which NF-κB activation is involved. . ."

As to more specific diseases, the specification, at page 5, line 16, through page 7, line 15, and page 12, line 11 through page 13, line 22, describes in detail that activation of the NF-KB pathway is involved in the pathogenesis of many specified diseases, including, for example, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis (claim 75) and cancer (claim 72).

It is again respectfully submitted that the Examiner has not met his burden to establish a reasonable basis to question the enablement set forth in the disclosure for the claimed method of treatment for these specific diseases, or diseases in which NIK/cγc interaction is involved (claim 69), or diseases in which NF-κB activation is involved (claim 70). There is no reason to believe that any disease in which NIK/cγc interaction is involved in the pathogenesis thereof would not be treatable by means of the claimed method.

Nonetheless, the Examiner, at the bottom of page 3 of the Office Action, maintains the rejections for the following reasons.

First, the Examiner argues that, although the specification discloses that the C-terminal fragment of NIK1 (consisting of SEQ ID NO: 18) binds a cγc in the yeast two-hybrid system and that a NIK1 and a cγc are co-immunoprecipitated from cells over-expressing these proteins (Examples 1-2), the specification "teaches that it is questionable as to whether the peptide of SEQ ID NO: 18 binds to a full-length cγc protein (Table1)." Applicants disagree.

The Examiner's interpretation of Table 1 is incorrect. Please note that all the representations of '+' signs in the tables are relative. For instance, in Table 1, the estimate of +/- means that the binding of full-length common gamma chain to

NIK fragment was relatively weaker than the binding of the ICD fragment 289-369, which is represented as +/-. Viewed in this light, it is clear that Table 1 does not provide results questioning whether the peptide of SEQ ID NO: 18 binds to a full-length cγc protein. This is simply not true.

Second, the Examiner argues that the specification fails to provide evidence that the peptide of SEQ ID NO: 18 will bind to any protein having the structure or activity of cγc. This too is incorrect. Applicants direct the Examiner's attention to Example 7 (on page 57), which shows the binding of a NIK c-terminus peptide (NIK624-947) (SEQ ID NO: 19) is '++++' with full-length common gamma chain. See also, the specification, at page 20, lines 9-10, which clearly discloses that the NIK624-947 (SEQ ID NO: 19) comprises the claimed peptide, SEQ ID NO: 18 (NIK640-720), and that the latter peptide contains the important cγc binding domain of NIK. Since the claimed peptide of SEQ ID NO: 18 (NIK640-720) contains the important cγc binding domain of NIK624-947 (SEQ ID NO: 19), then it stands to reason that it too would bind to cγc in the same manner as shown in Example for NIK624-947. No evidence has been presented by the Examiner to effectively rebut this position.

Third, the Examiner argues that he "fails to see where the specification teaches that the peptide of SEQ ID NO: 18 interferes with NIK/cγc interaction." In reply, though the

specification does not set forth an experiment, in which the NIK peptide of SEQ ID NO: 18 is used as a competitor to block NIK-common gamma chain binding, the specification, at for instance, Figure 5, clearly shows that the NIK c-terminus (comprising SEQ ID NO: 18) inhibits common gamma chain induced enhancement of NIK function. Thus, contrary to the Examiner's position, the specification does show that the NIK c-terminus, which comprises the important cγc binding domain of SEQ ID NO: 18, inhibits common gamma chain induced enhancement of NIK function, and consequently interferes with NIK/cγc interaction.

Fourth, in item (B) on page 4, the Examiner argues that though the specification establishes that the polypeptide of SEQ ID NO: 18 (the C-terminal fragment of NIK1) inhibits NIK-induced activation of NF-kB transcription, the specification states at paragraph [0158] that the C-terminal region of NIK binds with the N-terminal region of NIK, inactivates the kinase and competes with binding of the kinase to its substrates. The Examiner then questions how does one know that the effect of SEQ ID NO:18 on NIK is not a direct effect, independent of cγc?

In reply, the experiments in the specification do not establish that the peptide SEQ ID NO: 18 inhibits NIK induced NF-kB activation. Actually, the peptide of SEQ ID NO: 18 is not the c-terminal peptide fragment of NIK, which was used in the two hybrid screening and that was used as dominant negative NIK to

inhibit NF-kB activation described in the specification. Instead, as discussed above, the specification discloses that SEQ ID NO: 18 is actually the minimal common gamma chain binding region in NIK that was identified by deletion analysis. SEQ ID NO: 18 has the amino acids 640-720 of NIK, which is the NIK domain responsible for cγc binding.

Further, contrary to the Examiner's argument, this region, SEQ ID NO: 18, is not involved in binding to the NIK N-terminus. The negative regulatory domain of NIK in its C-Teminus is the region 847-947 (SEQ ID NO: 19) (Xiao G et al, J. Biol. Chem., Vol. 275, Issue 28, 21081-21085, July 14, 2000). Again, the specification discloses that the NIK624-947 peptide (SEQ ID NO: 19) comprises the claimed peptide, SEQ ID NO: 18 (NIK640-720) which contains the important cγc binding domain. Therefore, the concern that the effect of SEQ ID NO: 18 is not direct is irrelevant.

Fifth, in item (C) on pages 4-5, the Examiner seemingly asks whether Applicants are contending that all diseases mediated by NF-κB, or any specific disease mediated by NF-κB are necessarily diseases in which NIK and cγc interaction are involved? He also appears to ask how then do Applicants know which NF-κB mediated diseases involve NIK/cγc interactions?

In reply, Applicants do not contend that all diseases where NF-κB is involved are through NIK-common gamma chain

pathway. Common gamma chain is present in the interleukin receptors IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. Out of these, Applicants show that IL-2 and IL-15 signaling involves NIK. See for instance, page 44, lines 18-21 of the disclosure. Modulation of NIK-common gamma chain pathway is relevant for only those diseases which involve defects in NF-κB activation induced by these interleukins. Such would be clearly evident to one reading the claims in view of the disclosure in the specification.

Accordingly, at least with respect to the diseases that can be treated by means of the present invention, reconsideration and withdrawal of this part of this part of the rejection is respectfully urged.

Lastly, Applicants note that the current enablement rejection is silent as to the scope of the polypeptide to be administered, i.e., the variant peptide embodiment having at least 90% sequence identity, and the functional derivatives language in the claims. Instead, the current rejection appears to focus solely on the treatment aspect with respect to the diseases that can be treated by the present invention. Thus, it is presumed that the previous response fully addressed and overcame the part of the rejection with respect to the scope of the polypeptide to be administered. In the event that the Examiner intended to maintain this portion of the rejection, then

Applicants herein reiterate by reference the arguments set forth on pages 18-19 of the response filed March 24, 2009.

In particular, if the Examiner still contends that the claims are still too broad with respect to the functional derivative language, this part of the rejection is respectfully traversed. The description of functional derivatives in the specification makes clear that there it is a derivative of a functional group on the polypeptide that does not change the biological properties of the polypeptide. Further, it should be noted that those of ordinary skill in the art have very high degree of knowledge in the field. Those who formulate pharmaceutical compositions with polypeptides are well aware of many ways to derivatize a polypeptide without changing its activity in order to improve pharmacological properties for example. It is well within the skill of those of ordinary skill in the art without engaging undue experimentation to make any such derivative and if necessary to test it to see that it maintains its activity as is required by the claims.

Also, as discussed above, the specification discloses at least two peptides, peptide NIK624-947 (SEQ ID NO: 19), which comprises the claimed peptide, SEQ ID NO: 18 (NIK640-720). The specification also discloses that the latter peptide contains the important cγc binding domain of NIK. Indeed, the specification describes in detail the amino acids responsible for the

functional binding as required by the claims. Based on such, Applicants should be entitled to a reasonable degree of breadth of their invention. A person who invents the use of a polypeptide should not give free reign to an infringer who derivatizes it in a known manner in order to improve solubility for example. The Examiner has not explained why it would take undue experimentation to determine whether any given derivative falls within the scope of the claim. Accordingly, reconsideration and withdrawal of this part of the rejection is also respectfully urged.

Also, claims 102 and 104 specify that the functional derivatives are an ester or aliphatic amid of a carboxyl group and N-acyl derivative of a free amino group, or an O-acyl derivative of a free hydroxyl group. This is supported by the specification in the first paragraph of page 24. These claims should be free of this part of the rejection.

Furthermore, separate consideration should be given to claims 103 and 105, which exclude functional derivatives altogether.

In view of the above, it is respectfully submitted that the skilled artisan, upon reading the disclosure and in view of the knowledge in the art, could construct any of the limited number of peptide fragments of NIK, which comprise the cγc binding domain (SEQ ID NO: 18) and which maintain the ability

thereof to bind to cγc and inhibit cγc/NIK interaction or fragments or derivatives thereof having at least 90% sequence identity, as encompassed by claims, and then use them in the claimed methods to treat diseases in which NIK/cγc interaction is involved (independent claim 69) or in which NF-κB activation is involved (independent claim 70) or the other diseases listed (claim 75). Moreover, it is submitted that such could be done using the routine techniques and procedures disclosed in the specification without undue experimentation.

Withdrawal of the enablement rejection is requested.

IV. Written Description Rejection

Claims 69, 70, 75, 82, 83, 85-88, 90, 91, and 102-105 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description support for the reasons set forth in pages 5-6. The Examiner argues that the specification fails to describe a method for treating any disease using any variant of a NIK protein in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing.

This rejection is respectfully traversed for the same reasons set forth immediately above with respect to the enablement rejection and for the following reasons. See the discussion above for the support in the disclosure for the treatment of diseases utilizing the claimed method, as well, as

the support in the disclosure for the functional derivatives language with respect to the scope of the polypeptides.

In view of such disclosure, it is believed that those of ordinary skill in the art would understand that Applicants were in possession of the full scope of the claimed method of treatment, including the functional derivates subparagraph of the independent claims, as functional derivatives of active polypeptides are extremely well known in the art. Applicants are not making new discoveries with respect to functional derivatives but is merely claiming its polypeptides in a scope so as to include such derivates that are used for example to improve pharmacological properties.

Reconsideration and withdrawal of this rejection is therefore respectfully urged.

V. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance, and favorable action thereon is requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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